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Case Report

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Ponatinib-induced dilated cardiomyopathy: a case report.

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ABSTRACT

Ponatinib is a third-generation tyrosine kinase inhibitor with potent efficacy in the treatment of acute and chronic leukemia. Despite having an effective and sustained activity in all BCR-ABL1 mutations, it may cause cardiovascular adverse effects. Here we report a 56-year-old male patient with Chronic myeloid leukemia and no prior cardiac disorder who developed acute heart failure under ponatinib treatment. Guideline-recommended medical treatment for heart failure was initiated. Coronary angiography to exclude ischemic heart disease revealed no coronary stenosis. Cardiac magnetic resonance imaging showed findings consistent with non-ischemic dilated cardiomyopathy. After interruption of ponatinib treatment, cardiac evaluation showed improvement in left ventricular ejection fraction. Patients on Ponatinib therapy should be closely monitored for signs and symptoms of heart failure.

Keywords: Cardio-oncology, dilated cardiomyopathy, heart failure

INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by increased tyrosine kinase activity.[1] Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML. So far, multiple TKIs have been approved for the treatment of CML; however, TKI-related toxicities have long been known.[2] Ponatinib is a third generation TKI was approved by US Food and Drug Administration for CML in cases of resistance or intolerance to prior TKI therapy.[3] In this report, we present a 56-year-old male patient with CML and no prior cardiac disease who developed dilated cardiomyopathy after treatment with ponatinib.

CASE

A 56-year-old male patient presented with postprandial abdominal pain, diffuse abdominal tenderness, and new-onset bilateral lower extremity edema. The patient was diagnosed with CML in 2017 and treated with TKIs including imatinib, dasatinib, and nilotinib, however failed to achieve molecular and clinical response. As a result, the patient was switched to ponatinib due to resistant disease despite previous TKI treatments. After starting at a daily dosage of 45 mg, the patient achieved molecular and clinical response and has subsequently been maintained on a daily dose of 15 mg of ponatinib for four years. The patient's initial laboratory results indicated acute kidney injury with a creatinine value of 1.44 mg/dl. Additionally, the level of liver enzymes were elevated with alanine aminotransferase at 632 U/L, aspartate aminotransferase at 437 U/L, alkaline phosphatase at 418 U/L, gamma-glutamyl transferase at 399 U/L, and total bilirubin at 3.98 mg/dl. Abdominal ultrasound revealed no abnormalities, except for hepatomegaly. The concentration of brain natriuretic peptide was measured at 3227.2 pg/ml. Hepatic congestion and cardiorenal syndrome secondary to heart failure was suspected. Transthoracic echocardiography revealed a significant decrease in the ejection fraction (EF) to 25% compared to the patient's baseline EF of 55% before initiating ponatinib treatment. Ponatinib treatment was discontinued and replaced with guideline-recommended medical therapy consisting of ramipril 5 mg/day, spironolactone 25 mg/day, carvedilol 6.25 mg/day, and twice-daily administration of 40 mg of intravenous loop diuretic. A coronary angiogram was conducted to rule out ischemic heart disease, but no significant stenosis was detected. Cardiac magnetic resonance imaging (CMR) showed mid-myocardial fibrosis in the septum, contrast uptake in the papillary muscles at the basal segments, and diffuse interstitial fibrosis in other myocardial segments consistent with non-ischemic dilated cardiomyopathy (Figure). During hospitalization, there was an improvement in creatinine levels and liver

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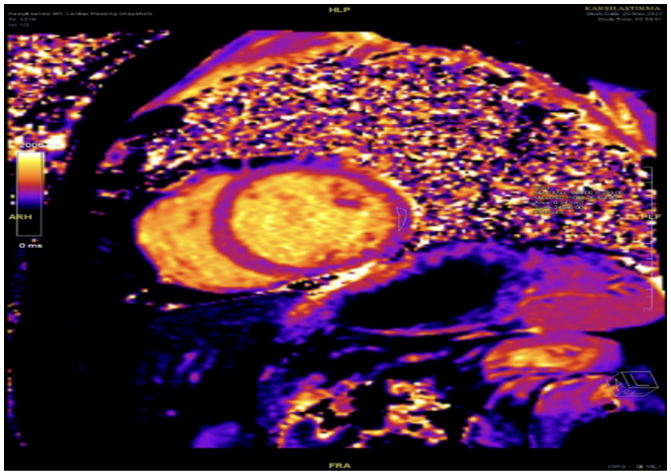

Figure. Cardiac magnetic resonance imaging (CMR) reveals mid-myocardial fibrosis in the septum, contrast uptake in the papillary muscles at the basal segments, and diffuse interstitial fibrosis in other myocardial segments.

enzymes, and the hypervolemic condition resolved. Follow-up echocardiography revealed the recovery of left ventricular function with an ejection fraction of 50%. The patient was discharged for continuation of current medical treatment and close follow-up. In the last visit, he was deemed ineligible for a stem cell transplantation due to several comorbidities. At present, the patient is not currently receiving any TKI and is being closely monitored on a monthly basis.

DISCUSSION

Dilated cardiomyopathy is defined as the presence of left ventricular dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions (hypertension, valvular disease, congenital heart disease) or coronary artery disease. According to the recently published 2023 European Society of Cardiology Cardiomyopathy Guideline, contrast enhanced CMR is recommended in all patients with suspected cardiomyopathy at initial evaluation.[4] In our patient, the absence of ischemic heart disease assessed through invasive angiography, the absence of valvular and congenital heart disease assessed through echocardiography, and the presence of left ventricular dilatation and systolic dysfunction, along with interstitial fibrosis and late gadolinium enhancement documented by cardiac MRI, indicated a "ponatinib-related dilated cardiomyopathy phenotype with midmyocardial fibrosis and low EF". Laboratory and clinical improvement after withdrawal of the implicated agent also supported the diagnosis.

Cardiovascular (CV) adverse events are considered common complications of ponatinib treatment. The safety of ponatinib have been evaluated in the Ponatinib Philadelphia chromosome–positive acute lymphoblastic leukemia and CML Evaluation.[5] The study highlighted the risk of arterial occlusion and CV adverse events in general in ponatinib-treated patients and shown that reducing the dose of ponatinib in certain settings can achieve optimal responses and reduce ponatinib-related CV events.[5,6] Pharmacokinetic analysis has indicated the possibility of reducing the starting dose of ponatinib to 15 mg/day and preliminary data showed advantages in terms of safety while maintaining its efficacy.[6]

Mechanisms leading to ponatinib cardiotoxicity are still not fully understood. Ponatinib is a potent inhibitor of various tyrosine kinases, including FGFRi, PDGFR and VEGFR.[7] Some studies suggested that multi-kinase inhibitor properties of ponatinib may play a role in cardiovascular complications by causing endothelial dysfunction.[8-10] Some in-vivo studies have demonstrated that ponatinib impairs AKT and ERK pathways which are important for cardiomyocyte survival.[11,12] Ponatinib associated inhibition of AKT and ERK pro-survival pathways and disruption of cardiac cells leads to left ventricle dysfunction and heart failure.[12] So, it is considered that ponatinib induced heart failure may be reversed after stopping ponatinib treatment, patients should be closely monitored for signs and symptoms of congestive heart failure.[13]

CONCLUSION

Ponatinib is associated with cardiac adverse events including vascular occlusion, myocardial infarction, and left ventricular dysfunction. Herein, we reported a patient developed dilated cardiomyopathy while receiving low dose ponatinib. To our knowledge, this is first case reported with dilated cardiomyopathy as an adverse event of ponatinib.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from the patients for the publication of the case report and accompanying images.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. de Klein A, van Kessel AG, Grosveld G, et al. A cellular oncogene is translocated to the Philadelphia chromosome in chronic myelocytic leukaemia. *Nature*. 1982;300(5894):765-767. doi:10.1038/300765a0
2. Pasvolsky O, Leader A, Iakobishvili Z, Wasserstrum Y, Kornowski R, Raanani P. Tyrosine kinase inhibitor associated vascular toxicity in chronic myeloid leukemia. *Cardio-Oncology*. 2015;1(1):1-10 doi:10.1186/s40959-015-0008-5
3. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. *N Engl J Med*. 2013;369(19):1783-1796. doi:10.1056/NEJMoa1306494
4. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44(37):3503-3626 doi:10.1093/eurheartj/ehad194
5. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*. 2018;132(4):393-404. doi:10.1182/blood-2016-09-739086
6. Cortes JE, Deininger MW, Lomaia E, et al. Three-year update from the optic trial: a dose-optimization study of 3 starting doses of ponatinib. *Blood*. 2022;140(1):1495-1497. doi:10.1182/blood-2022-157822
7. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. *Cancer Cell*. 2009;16(5):401-412. doi:10.1016/j.ccr.2009.09.028
8. Valent P, Hadzijusufovic E, Hoermann G, et al. Risk factors and mechanisms contributing to TKI-induced vascular events in patients with CML. *Leuk Res*. 2017;59:47-54. doi:10.1016/j.leukres.2017.05.008
9. Gover-Proaktor A, Granot G, Shapira S, et al. Ponatinib reduces viability, migration, and functionality of human endothelial cells. *Leuk Lymphoma*. 2017;58(6):1455-1467. doi:10.1080/10428194.2016.1239258

10. Gover-Proaktor A, Granot G, Pasmanik-Chor M, et al. Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib differentially affect the vascular molecular pathways and functionality of human endothelial cells. *Leuk Lymphoma*. 2019;60(1):189-199. doi:10.1080/10428194.2018.1466294
11. Singh AP, Glennon MS, Umbarkar P, et al. Ponatinib-induced cardiotoxicity: delineating the signalling mechanisms and potential rescue strategies. *Cardiovasc Res*. 2019;115(5):966-977. doi:10.1093/cvr/cvz006
12. Talbert DR, Doherty KR, Trusk PB, Moran DM, Shell SA, Bacus S. A Multi-parameter in vitro screen in human stem cell-derived cardiomyocytes identifies ponatinib-induced structural and functional cardiac toxicity. Toxicol Sci. 2014;143(1):147-155. doi:10.1093/toxsci/kfu215
13. Shelburne N, Adhikari B, Brell J, et al. Cancer treatment-related cardiotoxicity: current state of knowledge and future research priorities. *J Natl Cancer Inst*. Sep 2014;106(9):dju232 doi:10.1093/jnci/dju232